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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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QUARLES & BRADY LLP
411 E. WISCONSIN AVENUE
SUITE 2040
MILWAUKEE, WI 53202-4497

EXAMINER

SHUKLA, RAM R

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 09/25/2002

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/663,805

Applicant(s)

KIMBLE ET AL.

Examiner

Ram Shukla

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 26 June 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: *detailed action*

DETAILED ACTION

1. Claims 1-21 are pending in the instant application.
2. The attempt to incorporate subject matter into this application by reference to Friedman et al Proc. Nat. Acad. Sci. USA 97:4736-4741, 2000 is improper because the reference was published in April 2000, almost seven months after the effective filing date of the instant application. Therefore, an artisan of skill would not have had access to the teachings of the reference at the time of the effective filing date of the claimed invention.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claimed invention is drawn to a method of evaluating a test compound's ability to modulate prolyl-4-hydroxylase (P4H) by introducing a test compound into a test chimeric nematode, a P4H-gene modified nematode or a wild type nematode and observing change in dpy or embryonic lethal phenotype due to the test compound's effect on P4H. However the specification as filed does not provide sufficient guidance as to how an artisan of skill would have practiced the claimed invention without undue experimentation as discussed below.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement

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requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

First, the claimed invention encompasses any nematode, however, the specification does not teach how to produce any test chimeric nematode or P4H-gene modified nematode because nematode belong to phylum nematoda that comprises approximately 12,000 species that have very diverse physiology and metabolism. The specification does not provide sufficient guidance as to how an artisan of skill would have produced any nematode such as those that are parasites or free living or vary in length from less than a millimeter to 35 centimeters, have different body structure or other characteristics (see pages 509-516 in General Zoology Sixth Edition by Villee et al. Saunders College Publishing, 1984). Neither the specification nor the art of record teaches that any nematode would have the phenotype dpy or embryonic lethal when PH4 gene is mutated in the nematode. An artisan would have required undue experimentation to practice the claimed methods in any nematode since it is not routine any chimeric nematode or P4H modified nematode and the specification does not teach how to make the nematodes encompassed by the claimed invention.

Next, the issue is: is dpy phenotype or embryonic lethal phenotype specific to only PH4 gene? Levy and co-workers noted that the dumpy, nonroller, nondumpy, left roller and dumpy left roller phenotypes are caused by mutations in dpy-2, dpy-10, sqt-1, dpy-13 and rol-6 genes (Levy et al. Mol Cell Biol 4:803-817,

1993). In other words, if compound was added to a nematode (wild type or mutant), the nematodes may develop these phenotypes even if the compound did not affect P4H, rather these phenotypes could develop if the compound affected the dpy genes or sqt- gene or rol gene. Therefore, an artisan would not be able to discern whether the change in the dpy phenotype was due to change in what gene. Likewise, the embryonic lethal phenotype may be produced due to the inhibition of any essential gene that was crucial for development. Therefore, the specification does not teach as to how dpy or embryonic lethal phenotypes could be used for the claimed method with specificity.

Next, the issue is: what is a test chimeric nematode, a P4H-gene modified nematode and a complemented P4H gene mutation? While the specification teaches what is a chimeric nematode or a P4H-gene modified nematode, the specification does not teach as to how these nematodes will be produced. It is noted that the specification lists an article by the inventors in PNAS, however, the article is published in April 2000, whereas the effective filing date for the instant application is September 1999, which would indicate that the article was not available to an artisan at the time of the filing of the application. Accordingly, the teachings of the paper would not have been available to an artisan at the time of the filing of the application. Additionally, art of record does not teach how to make these nematodes. Accordingly, an artisan of skill would not have been able to make a chimeric nematode or a P4H modified nematode.

It is noted that post filing art Hill et al (Genetics 155:1139-1148, 2000) discloses that dpy-18 encodes an alpha-subunit of P4H hydroxylase in C.elegans. However, this art also brings about the difference between different collagen subtypes of C.elegans and vertebrates. Collagen is post-translationally modified by P4H.

Next, the question is: if a nematode had a mutated P4H gene, how would a compound increase the activity of P4H, unless the effect of the mutation could be reversed by the compound. However, it is unclear as to how the lack of P4H activity due to a mutation could be reversed due to a treatment with a compound. Regarding claim 12, it is noted that this claim recites that a compound is into an

animal that has a dpy-18 phenotype or poh-1 phenotype, however, if the phenotype is a dumpy phenotype, such a phenotype can be produced by mutation in several genes therefore, an artisan would not know whether rescue of the phenotype is due to rescued dpy-18 activity or any other gene. Again, it is unclear as to how a compound can rescue the dpy-18 or poh-1 phenotype unless the compound can reverse the effect of the mutation in the genes.

Next the question is: can a human P4H gene or P4H gene of any other organism rescue the P4H activity in a dpy-18 or another mutant nematode? There is no evidence of record that a human P4H could rescue the nematode P4H activity. Hill et al (Genetics 155:1139-1148, 2000) discloses that dpy-18 encodes an alpha subunit of P4H in C.elegans, however, these investigators also indicated that there is significant difference between the C.elegans collagens and vertebrate collagen (see the first full paragraph in the right column on page 1139 continued in the left column on page 1140), therefore, it is not clear that a vertebrate P4H will be able to rescue a mutant P4H in C.elegans or any other nematode. There is no evidence of record to indicate so and the examples shown in the specification did not use a complementation of the P4H activity in a mutant nematode. Veijola et al (Journal of Biological Chemistry 269:26746-26753, 1994) also isolated a cDNA that encoded P4H alpha subunit of C.elegans and the C.elegans alpha subunit made a heterodimer with human beta subunit, however it's structure and function were different from the heterodimer of human alpha and beta subunits (see second paragraph in the right column on page 26746 and last two paragraphs in the left column on page 26752). This clearly indicates that while a human P4H subunit may associate with a nematode subunit, it is not questionable whether a human P4H subunit can complement nematode P4H function.

Next, regarding claim 9 it is noted that in view of the discussion that the dpy phenotype was not specific to P4H gene, it is not clear as to when a wild type nematode is treated with a test compound, how would an artisan know that the activity of P4H (dpy-18) on chromosome III was modulated and not that of any other gene such as dpy-2, dpy-10, sqt-1, dpy-13 and rol-6.

In conclusion, the specification does not provide sufficient guidance as to how an artisan of skill would have made the claimed invention in view of the issues raised above. An artisan of skill would have required extensive experimentation to address the issues raised above and such experimentation would have been undue since such experimentation was not routine in the art and the specification does not provide necessary guidance how to address the issues raised above.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it is unclear as to what is encompassed by the phrase "a complemented prolyl-4-hydroxylase gene mutation". The specification fails to describe the definition for the phrase.

Claim 3 recites the limitation "the inhibitor" in line 1. There is insufficient antecedent basis for this limitation in the claim because neither claim 3 nor the independent claim 1 recites the limitation "an inhibitor".

Claim 8 is vague and indefinite because it unclear as to what is meant by "the test chimeric nematode is a C.elegans and is a dpy-18 mutation". It is unclear as to how can a C.elegans be a mutation.

Claim 12 recites the limitation "the test nematode" in line 6. There is insufficient antecedent basis for this limitation in the claim does not recite the limitation "a test nematode".

Claim 17 is vague and indefinite because it is unclear as to what is encompassed by the phrase "a complemented prolyl-4-hydroxylase gene mutation". The specification fails to describe the definition for the phrase.

Claim 17 recites the limitation "the test nematodes" in line 7. There is insufficient antecedent basis for this limitation in the claim because claim 17 does not recite the limitation "a test nematode".

Claim 19 recites the limitation "the nematode" in line 1. There is insufficient antecedent basis for this limitation in the claim does not recite the limitation "a nematode".

Claim 20 recites the limitation "the nematode" in line 1. There is insufficient antecedent basis for this limitation in the claim because neither claim 20 nor claim 19 recites the limitation "a nematode".

Claim 10 recites the limitation "the nematode" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 10 does not recite the limitation "a nematode".

Claim 11 recites the limitation "the nematode" in line 1. There is insufficient antecedent basis for this limitation in the claim because neither claim 10 nor claim 11 recites the limitation "a nematode".

Claim 13 recites the limitation "the nematode" in line 1. There is insufficient antecedent basis for this limitation in the claim because neither claim 12 nor claim 13 recites the limitation "a nematode".

Claim 14 recites the limitation "the nematode" in line 1. There is insufficient antecedent basis for this limitation in the claim because neither claim 13 nor claim 14 recites the limitation "a nematode".

7. No claim is allowed.
8. The invention of claims 1-21 is free of the prior art of record.

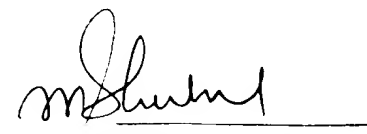
When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to **§** 1.121(c). For instructions, Applicants are referred to <http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm>.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.


RAM R. SHUKLA, PH.D
PATENT EXAMINER